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ON THE CAUSES OF EDEMA.

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Nothing is more common in science, and particularly in medical science, than to find it necessary to take up old ideas that had long been believed firmly fixed in fact and examine anew into their reasonableness, very often with the result that we find our premises have been untenable and our conclusions wrong. The subject on which I will venture to speak—the cause of edema—presents such a case. Once regarded as one of the simplest pathological phenomena, now it is admitted to be one of the most complex—one in whose explanation must be involved the interpretation of a large proportion of the vital processes both of health and disease. To avoid obscurity in discussing the less familiar parts of this subject, I must crave your patience while rehearsing some facts long since known to you.

The discovery of the circulation of the blood is rightly accounted the most gigantic stride that has ever been made in the advancement of physiology, and through it of clinical medicine. But the circulation of the blood itself is but the half a concrete subject, and, considered alone, is almost without importance. In the higher animals the blood fluid is retained within the closed system of blood vessels. The protoplasmic elements of the living tissues are outside the blood vessels, and it is to nourish them that the blood exists. It has long been known that the tissues are directly fed by a fluid—the lymph—which escapes from the blood through the walls of the vessels and which is chemically nearly allied to the blood plasma. Once outside the blood vessel and bathing the tissue elements, lymph is supposed to enter the protoplasm of the latter under the moving force of osmosis, and by the same law the poisonous

Presented by the author



products of tissue change, pass out of the protoplasm and enter the lymph vessels, by which they are brought again into general circulation. It is evident, then, that notwithstanding the meagerness of our knowledge regarding it, the circulation of the lymph has an importance paramount with that of the blood itself. Most important of all is that wonderfully complex *tissue circulation*, as we may call it, of the lymph, which is outside both the blood and lymph vessel, and which is on its way to give up food to the protoplasm or to remove wastes from it.

Recent researches have established the fact of chemotaxis—that certain leucocytes and other phagocytic corpuscles are attracted by and accumulate in the neighborhood of definite chemical materials introduced into the body, while other chemical compounds have the reverse effect and repel the approach of the wandering phagocytes. It is by no means absurd to assume, as a working hypothesis, that, contrariwise, the living tissue protoplasm itself exerts an attractive or a repulsive force—a positive or a negative chemotaxis, for certain chemical compounds, by means of which it draws the food and repels the waste matters. Until recent years, the origin of the lymph from the blood, its amount and quality, seemed a simple matter. By the known laws of osmosis some of the blood plasma must escape through the vessel walls by reason of the chemical changes produced in the lymph by the tissue elements, since, in general, chemically different fluids diffuse into each other. Moreover, the blood within the capillaries is under a positive pressure, which, presumably, would be sufficient to cause an excess of transudation in the direction of the lymph spaces and tissues. Then, again, the well known fact that in a functionally active organ the arteries are dilated and the pressure within the capillaries is increased, seemed to account in a satisfactory way for the accelerated transudation of lymph under these conditions. Here is a field, however, in which the facts of pathology have corrected the theories of physiology. In healthy life the ratio of the rate of transudation through the walls of the blood vessels to that of the removal of lymph from

the tissues, varies only within narrow limits, so that at any time only enough lymph is found within the tissues to fairly moisten them. Let the ratio of transudation to that of lymph removal be decreased and we would find the tissues dessicated. Let the ratio be increased and we find edema; for it can hardly be doubted that in edema the excess of fluid within the lymph spaces has come from the blood, although chemically the character of the edema fluid may differ widely from that of normal lymph.

Looked at from an *a priori* standpoint at least the following factors may be considered to participate in the production of edema:

1. The quality of the blood; experiments on osmosis make it certain that every substance in solution has a specific rate of diffusion through membranes, and it is not difficult to imagine that the diffusion coefficient of the blood varies from the quality of the fluid.
2. The blood pressure; the idea is firmly fixed that the transudation of lymph is in some way proportional to the intravascular pressure.
3. The character of the diffusion membrane, *i. e.*, the wall of the blood vessel, which in this case is limited chiefly to the endothelial cells which, joined edge to edge, form the walls of the capillaries.

That the character of the blood may have to do with the production of edema, the clinical phenomena of anemia and the experimental results from the injection of dilute saline fluids into the circulation, indicate. Certain organic compounds introduced into the blood are said to have a remarkable power in causing edema. But edema does not occur in any of these until the character of the circulating blood is profoundly altered. As will be seen later on, there are reasons for believing that the edema so produced is a result rather than the effect of the altered blood on the vitality of the lining endothelium than of a change in its osmotic equivalent. The view so long held, that blood pressure alone was the principal factor in the production of edema has been so clearly disproved by clinical observation and physiological experiment that it can no longer be considered tenable; no known increase of arterial blood pressure can cause edema in a healthy vascular circuit.

For a number of years the conception has been developing, until now it is formulated as an expression of belief, by the foremost students of physiology and pathology, that the wall of the blood vessel is not the passive diffusion membrane it was once taken to be, but that it, at least as regards its endothelial lining, is a living organism, or group of organisms, of certain definite powers, and extremely sensitive to changes in its environment. This living vascular endothelium is the diffusion membrane through which the blood plasma must ooze to replace the lymph. These endothelial cells, when healthy, allow the transudation to occur at a certain definite rate, and provide that substances shall pass through them in fixed proportion. Let, however, these endothelial cells be subjected to adverse influences, particularly to poisonous matters circulating in the blood, and the normal resistance to the transudation of certain compounds, and their regulation of the percentage composition of the transudate is diminished, and edema, with more or less abnormal chemistry of the exudate, is the result. Indeed, there are accumulating reasons for believing that, not only is the living capillary wall endowed with selective power over the quantity and qualities of the materials passing through it under the hypothetical action of the law of osmosis, but that this transference of fluid is not a simple process of osmosis and transudation but of true secretion, under the control of secretory nerves. If a glass tube be placed in a duct of the submaxillary gland and the chorda tympani nerve be laid bare and cut, no disturbance will follow, but if the peripheral end of the cut nerve that connected with the gland be laid upon the electrodes and irritated, at once the gland reddens, pulsates, and a rapid stream of saliva flows from the tube in the duct, under a pressure, too, which may be greater than that of the blood in the carotid artery. The only obvious explanation of the result is that the nervous impulses traveling down the chorda tympani have caused the gland cells to actively absorb fluid from the lymph bathing them and to forcibly pass it into the duct of the gland. Heidenhain, perhaps the ablest investigator of this subject, appears

to be of the opinion that transudation through the vessel walls is, like that through the cells of the submaxillary gland, an act of secretion under the control of secretory nerves. If this be true, we must look, of course, for vascular secretory nerve centres, and for afferent nerves by whose irritation transudation may be reflexly excited. Whatever be the truth of this particular hypothesis, it is a significant fact, that in dogs venous stagnation produced in the posterior extremities, by ligation of the vena cava, causes no edema except when the vasomotor nerves are divided; when the sciatic nerve, for example, is cut on one side, there is edema on that side but not on the other. The general statement seems indisputable that normal transudation can occur only through healthy vascular endothelium, and that the conditions which produce edema are conditions which lower the vitality of that endothelium. The meaning of the various clinical precursors of dropsy and edema, such as impoverishment of the blood, as in chlorosis, obstruction to the circulation, as in cirrhosis of the liver, deterioration in the quality of the blood, as is probable in nephritis, local inflammation, septic and non-septic, in each case, seems clear, and edema seems to be the natural pathological result, when we consider these conditions as provoking vital changes in the living cell wall through which the fluid must pass.

More than four years ago the author of this paper carried on a series of experiments with a view of arriving at a scientific treatment of uremia. It was assumed that the phenomenon known as uremic coma and convulsions were due to the accumulation in the body of definite, diffusible chemical compounds of poisonous nature. It was thought that if the abdominal cavity of an animal suffering from uremia were flushed with large quantities of warm, dilute salt solution, the poisonous matters would diffuse through the walls of the abdominal vessels with sufficient rapidity to sensibly reduce their toxic effect; for, surely, the thinness and extent of the surface of the walls of the abdominal vessels make of them a diffusion membrane of unparalleled efficiency. The experiments were per-

formed on some half dozen dogs. The renal arteries were laid bare and ligated in each case and the external wounds closed. The waste matters usually excreted by the kidneys were thus caused to accumulate within the body. The surgical procedure *per se* was marked by no result; but after a remarkably constant period, at the end of about thirty hours, the dogs were found manifesting in a decided manner the phenomena of uremia, now coma, now typical convulsions, and so they died. In some instances the abdominal cavity was flushed after the onset of the symptoms of uremia; in one case the flushing was begun before the signs of poisoning appeared. The results were altogether negative; in no instance was there the least ground for the belief that the onset of death had been delayed by the flow of fluid over the abdominal viscera. The outcome of the experiments, then inexplicable, now seems clear; for the walls of the blood vessels are *living* diffusion membranes; their vitality regulates osmosis through them; the results expected from the experiments tried could only have been logically anticipated from the use of dead diffusion membranes.

Through experiments on living animals at least two ways have been determined in which the vitality of the vascular endothelium may be affected. 1st. Directly under the influence of certain poisons. Thus Wooldridge, as quoted by Horsley, showed that when both femoral veins were tied no edema resulted, but if into the vessel of one leg a small quantity of what he called "tissue fibrinogens" were injected, abundant edema occurred in that leg. It is not hard to believe that, in the edema of local infection the ptomaines resulting from bacterial activity are the potent factors in producing the swelling through their influence on the endothelium. And even in aseptic wounds we have certain cells dying and giving off death products, which, perhaps, act as poisons on the still living endothelium. 2d. Perhaps a more important cause of edema is the reduction of the vitality of the endothelium by starvation. Any interference with the flow of blood through an arteriole must diminish the amount of nutritive material passing into the capillaries

arising from it. When we consider the extreme sensitiveness of protoplasm to even a momentary failure in its supply of oxygen, it is not difficult to conceive a slight stagnation or even reduction in the volume of the circulating blood current sensibly affecting the permeability of the endothelium. Thus it has been repeatedly found that clamping the renal artery for a few seconds is marked by the appearance of albumin in the urine, and this albuminuria not only accompanies the urinary flow which occurs on opening the artery, but is coincident with the small amount of secretion produced during arterial closure. On the other hand, no simple increase of blood pressure in the kidney has ever been found to cause albuminuria. It seems to be the present tendency among pathologists to ascribe to vascular anemia alone, without regard to subsequent increase of blood pressure, the occurrence of this group of edemas. The writer ventures to express, however, an opinion arrived at more than five years ago, that though the primary condition making edema possible is to be found in the local anemia, it is the subsequent increase of intra-vascular pressure due to the full inflow of the blood current, that makes the edema actual and evident.

Long ago Marey made a physiological observation of great importance in this connection, namely, that on rising in the morning a person's feet are larger in size than later in the day. People to whom the size of the feet is a consideration are well aware that their tightest boots cannot be put on in the morning. The explanation seems plausible that the vascular endothelium of the lower extremities had, during the sleeping hours, been adjusted to withstanding a certain transudation pressure, much less than that experienced in the upright position; when, therefore, the erect position is assumed, it requires time for the vascular protoplasm to adjust itself to the new mechanical conditions and support the column of blood. Again, Senator holds that the occurrence of physiological albuminuria is a fact and points out that traces of albumin in the normal urine may be looked for in the hours of the forenoon only. It is probable that, during the night, the kidneys

are comparatively anemic ; the events of awakening, rising and eating breakfast no doubt greatly increase the blood pressure in the kidney, and, according to the idea just expressed, this would explain the passage of albumin through the coils of the glomeruli for such a time as would be necessary to enable the glomerular cells to react to the changed mechanical conditions. At this day any theorizing which cannot be submitted to the test of experiment must be looked on with great distrust ; still, from the foregoing considerations there is an evident and attractive explanation of the close relation existing between the fluctuations in external air temperature and the origin of various inflammatory diseases. A sudden contraction of the surface blood vessels would drive the blood into interior organs, previously relatively anemic. On the same principle which accounts for the swollen feet in the morning, these internal organs would be rendered edematous and, therefore, less resistant to the onslaught of pathogenic micro-organisms, and we might reasonably expect a pneumonia, a pleurisy or an enteritis. Again, it is an hypothesis that has some support in observation, that a vascular area thus once subjected to the influences which produce edema, falls progressively more and more easily under control of such forces, and we may find herein the explanation of various chronic effusions. I desire to make the point, which facts appear to support, that edema, in a limited degree, is a frequent occurrence in normal tissues supplied by normal vascular machinery, and that this edema is a result of an increase of local blood pressure succeeding a period of comparative anemia. The whole conception turns on the view that the protoplasm of the vessel wall, either directly or indirectly through the medium of nerve centres, normally adjusts its resistance to transudation to the intra-vascular pressure prevailing ; with an increase of pressure there must be a new adjustment to prevent excessive transudation, and this adjustment comes about more slowly the longer the condition of low pressure has persisted and the more profound has been the condition of anemia.

In laboratory and clinic, this great subject in engaging the thoughts of able workers the world over, and there seems to be in the air a whisper that we shall, ere long, be able to grasp a generalization that will knit together and explain many now obscure facts in medicine.